

PCT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Thomas F. MEYER et al

Serial No.: 09/284,233

Filed: April 12, 1999

For: *HELICOBACTER PYLORI* LIVE VACCINE



INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner
for Patents
Washington, DC 20231

June 8, 1999

Sir:

In compliance with applicant's duty of disclosure under 37 CFR 1.56, enclosed are copies of material information of which applicant is aware, and which may be relevant to the above-identified application.

We have been advised that the applicants' German patent attorneys have conducted an extensive search to identify references relevant to the present application. The German patent attorneys furnished us with the following comments:

WO 94/24291

discloses attenuated *Salmonella* cells serving as a carrier for a heterologous antigen, for example, antigenic determinants from *Plasmodium*. In particular, the antigen is a fusion protein from hepatitis B virus core antigen and an antigenic determinant from *Plasmodium* (cf. claims 1 and 2). No *Helicobacter* antigens are disclosed.

U.S. 5,811,105

relates to a vaccine comprising a pharmaceutically acceptable carrier and an attenuated bacterium, wherein attenuation is effected by mutations in two discrete *aro* genes. The bacterium can be a *Salmonella* bacterium. No *Helicobacter* antigens are disclosed.

EP 0 863 211 A1

describes a fusion protein and a vaccine composition comprising said fusion protein or an attenuated cell expressing said fusion protein. The attenuated cell may be *Salmonella*. The fusion protein consists of a first immunogenic polypeptide which is used as an adjuvant, particularly tetanus toxin fragment C, and a second polypeptide fused thereto, against which an immune response is to be elicited. On page 3, lines 8-24 a great number of such second polypeptides is identified, however, there are no *Helicobacter* antigens.

WO 97/12909

relates to novel membrane proteins from *Helicobacter pylori* but does not include any indication of a live vaccine, wherein a recombinant, attenuated microbial pathogen expresses a *Helicobacter* antigen. The application discloses the treatment or prevention of a *Helicobacter* infection by administration of a subunit vaccine comprising isolated proteins (cf. page 9, lines 33 to page 10, line 12).

WO 86/01829

refers to a method of preparing an avirulent strain of a microbial pathogen and to a vaccine containing a corresponding strain. This document does not disclose any hint that a thus attenuated strain could be used as a carrier for a heterologous antigen, and there is no hint at *Helicobacter* antigens.

WO 97/14782

was published after the priority date of the present application and concerns live attenuated vaccine strains against gram-negative enteric pathogens which have a deficiency in expressing homologous O-PS and the capability of expressing heterologous O-PS covalently coupled to the LPS core. The expression products of said genes, however, would be located inside the cell and thus would not qualify for a heterologous antigen. *Helicobacter pylori* is mentioned as an enteric pathogen in the first paragraph of page 2, however, no live vaccine expressing a heterologous *Helicobacter* antigen is mentioned. On the contrary, it is suggested on page 14, last paragraph, to use the *Helicobacter* strain modified according to this document as a vaccine strain.

U.S. 5,583,038

discloses a recombinant mycobacterium transformed with DNA encoding a polypeptide, said polypeptide comprising a lipoprotein secretion signal sequence and a heterologous antigen. The antigens are derived from *Borrelia burgdorferi*, and there is no indication of *Helicobacter* antigens.

WO 86/03123

is concerned with live vaccines and, in particular, *Salmonella* exhibiting two non-reverting auxotrophic mutations. These vaccines may also be used as carriers for heterologous antigens. On page 17, line 30 to page 19, line 23 a multitude of suitable antigens and corresponding organisms are listed,

however, *Helicobacter* is not mentioned.

WO 96/14087

relates to a method of inducing an immune response to a tumor-specific antigen. This document does not include any indication of an attenuated microbial pathogen as carrier nor of a *Helicobacter* antigen.

WO 95/20665

discloses a vaccine composition comprising an attenuated bacterium and a pharmaceutically acceptable carrier. The attenuated bacterium comprises a DNA sequence under the control of an in vivo inducible promoter (the *htrA* promoter) which codes for one or several heterologous proteins. No *Helicobacter* antigens are disclosed.

WO 96/10421

pertains to a vaccine composition comprising influenza virus antigens and a mucosal adjuvant, namely chitosan. No *Helicobacter* antigens or live vaccines are disclosed.

WO 94/19482

is concerned with a bacterial chromosome containing a DNA sequence which encodes a heterologous antigen under the control of an iron-regulated promoter. The document discloses a cell containing said chromosome and a vaccine containing said cells. A multitude of heterologous antigens is listed on page 5, lines 4-23, but there is no indication of *Helicobacter* antigens.

WO 96/34624

corresponding to scientific publications Ferrero et al. (PNAS 92 (1995) 6499-6503) and GUT 37 (1995) A51, cited in Telford and Ghiara, *Drugs* 52: 799-804 (1996)

are concerned with a composition comprising a mixture of *Helicobacter* antigens consisting essentially of UreB and HspA of *H.pylori*, provoking a mucosal response. However, these data cannot be compared directly with the data of the present application, mainly because the recombinant antigen was administered in combination with a highly toxic adjuvant, namely cholera holotoxin. The use of these toxic adjuvants has severe disadvantages and renders the vaccine unsuitable for administration to humans.

Michetti et al. (*Gastroenterology* 107 (1994) 1002-1011) and Corthésy-Theulaz (*Gastroenterology* 109 (1995) 115-121) both use several repeated infections with recombinant *H.pylori* antigens (urease) in combination with cholera toxin as well as an infection with *Helicobacter felis*. None of these documents discloses results comparable with the results shown in the present application.

WO 94/03615 and WO 94/24291

are concerned with attenuated *Salmonella* strains with an inducible promoter for expressing heterologous antigens. These documents do not suggest the *Helicobacter* live vaccine according to the present invention. However, at the priority date of the present application, it was entirely unexpected and unpredictable that the live vaccine approach by recombinant *Salmonella* would lead to protection against *Helicobacter*. Thus, it becomes clear that the prior art on the priority date of the present application did not give a skilled artisan a clear and definite hint as to the subject matter of the present application but, due to the special characteristics of *Helicobacter*, even led him away from the subject matter of the present application. This is also supported by the documents

Eaton and Krakowka (*Gastroenterology*) 103 (1992) 1580-1586) and Lee and Buck (*Alimentary Pharmacology and Therapeutics* 10 (1996) Suppl.1: 129-138)

Eaton and Krakowka show that oral vaccination with *H.pylori* cannot prevent subsequent infection with viable *H.pylori* pathogens. Lee and Buck, again, describe the problems of the toxic mucosal adjuvants used in the prior art in the case of application in humans.

Developments Biol.Stand. 84 (1995) 211-219 gives no instructions how to develop an efficacious recombinant bacterial live vaccine against *H.pylori*, but refers generally to the history of live bacterial vaccines.

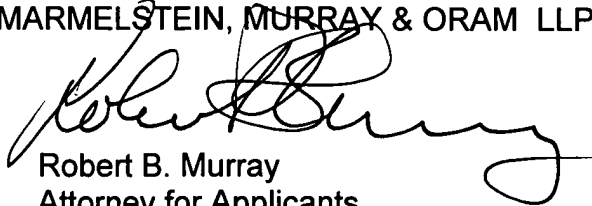
The majority of these additionally identified documents describes recombinant live vaccines, among others also attenuated *Salmonella* carrier cells expressing heterologous antigens. The expression of *Helicobacter* antigens in an attenuated microbial pathogen is neither disclosed nor rendered obvious by these prior art documents.

It should be noted that the undersigned has not made an independent review of the attached references to determine the accuracy of the German patent attorneys comments.

A copy of each reference and a PTO-1449 are attached.

In the event there are any fees due in connection with the filing of this paper, please charge our Deposit Account No. 14-1060

Respectfully submitted,
NIKAIDO, MARMELESTEIN, MURRAY & ORAM LLP

A handwritten signature in black ink, appearing to read "Robert B. Murray", is written over the printed name and firm name.

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Enclosure: References (21)
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